DOI 10.1002/mnfr.200500154 Mol. Nutr. Food Res. 2006, *50*, 152 – 159

Review

Intracellular signaling network as a prime chemopreventive target of (–)-epigallocatechin gallate

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Chemoprevention is an attempt to use either naturally occurring or synthetic substances or their mixtures to intervene in the progress of carcinogenesis. Recently, it has been shown that some edible phytochemicals alter gene expression, directly or indirectly, thereby regulating the carcinogenic processes. (–)-Epigallocatechin gallate (EGCG), a principal antioxidant derived from green tea, is one of the most extensively investigated chemopreventive phytochemicals. EGCG has been known to block each stage of carcinogenesis by modulating signal transduction pathways involved in cell proliferation, transformation, inflammation, apoptosis, metastasis and invasion. This review addresses the molecular target-based chemoprevention with EGCG by focusing on the common events mediated by transcription factors, such as NF-kappa B, activator protein-1 and nuclear factor erythroid 2 p45-related factor, and upstream kinases involved in the cellular signaling network.

Keywords: Antioxidant / Chemoprevention / Epigallocatechin gallate / Signaling / Green tea

Received: September 7, 2005; revised: December 1, 2005; accepted: December 1, 2005

1 Introduction

Chemoprevention is an attempt to use either naturally occurring or synthetic substances or their mixtures to intervene in the progress of carcinogenesis. A vast variety of phytochemicals present in our daily diet, including fruits, vegetables, grains and seeds, possess substantial anti-mutagenic and anti-carcinogenic activities. Recently, attention has been focused on common dietary chemicals that act on genomic DNA, directly or indirectly, thereby altering the expression of genes involved in malignant transformation or its protection [1]. In this context, it has become an important issue to identify signaling molecules associated with each stage in the natural history of cancer as prime targets of chemopreventive phytochemicals.

Green tea is one of the most popular and widely consumed beverages and represents a promising dietary source of chemopreventive and chemoprotective phytochcemicals [2–4]. Many epidemiological studies suggest a protective role of green tea consumption against development of various types of cancers. Thus, tea drinking has been associated with a reduced risk of stomach [5], pancreatic and colorectal cancers [6], and with decreased recurrence of stage I and II breast cancer [7]. Phase I and II clinical trials were performed with green tea extract as an anti-cancer regimen [8, 9].

Epigallocatechin-3-gallate (EGCG) is one of the most abundant polyphenols present in green tea. Other catechins present in green tea include epigallocatechin, epicatechin gallate and epicatechin. Chemopreventive or anti-tumor effects of these green tea polyphenols, particularly EGCG, have been studied extensively in the chemically induced rodent carcinogenesis models as well as several types of cancer cells in culture [10–12]. EGCG has been known to block or reverse the multi-step carcinogenesis by modulating the expression or activation of intracellular signaling network molecules responsible for carcinogenesis processes. This review deals with effects of EGCG on multi-

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Abbreviations: AP-1, activator protein-1; **ARE/EpRE**, antioxidant/electrophile response element; **COX**-2, cyclooxygenase-2; **EGCG**, epigallocatechin-3-gallate; **EGFR**, epidermal growth factor receptor: **ERK1/2**, extracellular signal regulated kinase 1/2; **IL**, interleukin; **JNK**, c-Jun NH_2-terminal kinase; **LPS**, lipopolysaccharide; **MAPK**, mitogen-activated protein kinases; **MMP**, matrix metalloproteinase; **NF-λB**, NF-kappa B; **Nrf2**, nuclear factor erythroid 2 p45 (NF-E2)-related factors; **PMA**, phorbol-12-myristate-13-acetate; **ROS**, reactive oxygen species; **Stat3**, signal transducer and activator of transcription 3

stage carcinogenesis and its underlying molecular mechanisms.

2 Cellular signaling molecules in multi-stage carcinogenesis

Carcinogenesis is generally recognized as a multi-step process in which distinct molecular and cellular alterations occur. Initiation is a rapid and irreversible process, which includes the uptake of a carcinogenic agent and its distribution and transport to organs and tissues where metabolic activation and the covalent interaction with target cell DNA occur, leading to genotoxic damage. The blockade of genotoxic damage constitutes the first line of defense against carcinogenic insults. This can be achieved either by reducing the formation of reactive carcinogenic species or by stimulating their detoxification through induction of phase-II enzymes. The phase-II detoxifying or antioxidant enzymes are important components of the cellular stress response whereby a diverse array of electrophilic and oxidative toxicants can be removed from the cell before they are able to damage target cell DNA.

In contrast to initiation, tumor promotion is considered a relatively lengthy and reversible process in which actively proliferating preneoplastic cells accumulate. It has been known that inflammation is deeply involved in the promotion stage of carcinogenesis [13–15]. Progression, the final stage of neoplastic transformation, involves the gradual conversion of premalignant cells to the neoplastic ones with increased invasiveness and metastatic potential. The transcription factors, such as nuclear factor kappaB (NF-κB) and activator protein 1 (AP-1), are transiently activated to regulate target gene expression in response to extracellular stimuli through specific intracellular signal transduction pathways.

3 Chemopreventive effects of EGCG

3.1 Inhibition of carcinogen activation or induction of phase-II detoxifying enzymes

Antioxidants exert chemopreventive activities not only by scavenging reactive oxygen species (ROS) but also by inducing *de novo* expression of genes that encode detoxifying/defensive proteins, such as glutathione peroxidase, gamma-glutamylcysteine synthetase, NAD(P)H:quinone reductase, heme oxygenase-1 (HO-1), *etc*. EGCG suppresses the oxidative DNA damage or cytotoxicity, induced by tobacco-specific nitrosamine [16], UV [17], and H_2O_2 or *N*-methyl-*N*′-nitro-*N*-nitorsoguanidine [18] in mouse lung, mouse skin, Chinese hamster V-79 cells, respectively. Protective effect of EGCG was associated with reduced generation of ROS, decreased lipid peroxidation, and maintenance of intracellular glutathione [19]. This antioxidative activity was correlated with inhibition of UVB-induced phosphorylation of ERK1/2, c-Jun NH_2-terminal kinase (JNK), and p38 [20]. Moreover, EGCG inhibited the TCDD-induced binding of the AhR to DNA and subsequent transcription of CYP1A1, which catalyze the metabolic activation of diverse chemical carcinogens, particularly polyaromatic hydrocarbons [21].

In addition, EGCG prevented UV-induced depletion of glutathione and suppression of glutathione peroxidase activity in human skin [22] and hairless mouse skin [20], thereby protecting against photocarcinogenesis. EGCG also restored detoxifying enzymes such as GST, glutathione peroxidase, superoxide dismutase and catalase that were depleted as a result of 7,12-dimethylbenz[a]anthracene treatment in mouse skin *in vivo* [23]. Activation of these enzymes was accompanied by significant attenuation of lipid peroxidation. The molecular mechanism underlying antioxidant enzyme induction by EGCG remains largely

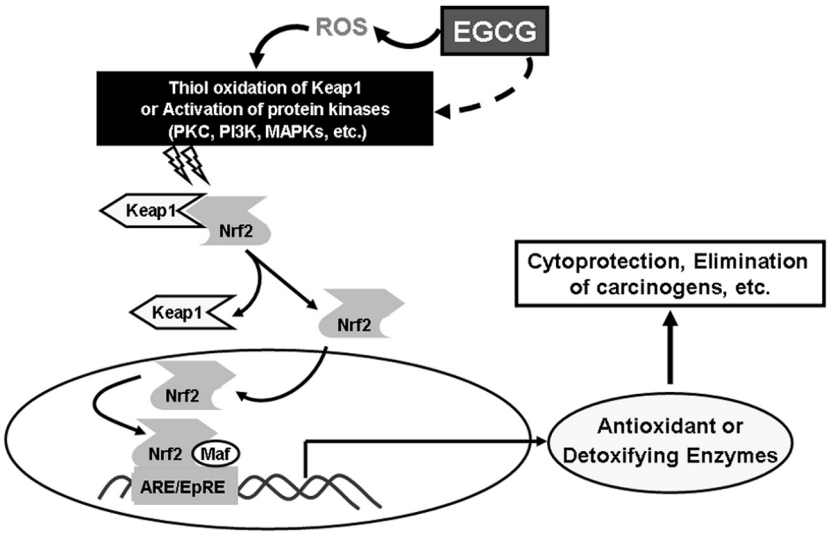

Figure 1. EGCG-induced upregulation of antioxidant or detoxifying enzymes via Nrf2–ARE signaling. EGCG may activate Nrf2 through phosphorylation of Nrf2 by upstream kinases and/or oxidation of Keap1 cysteine thiols, which facilitate the release of Nrf2 from Keap1.

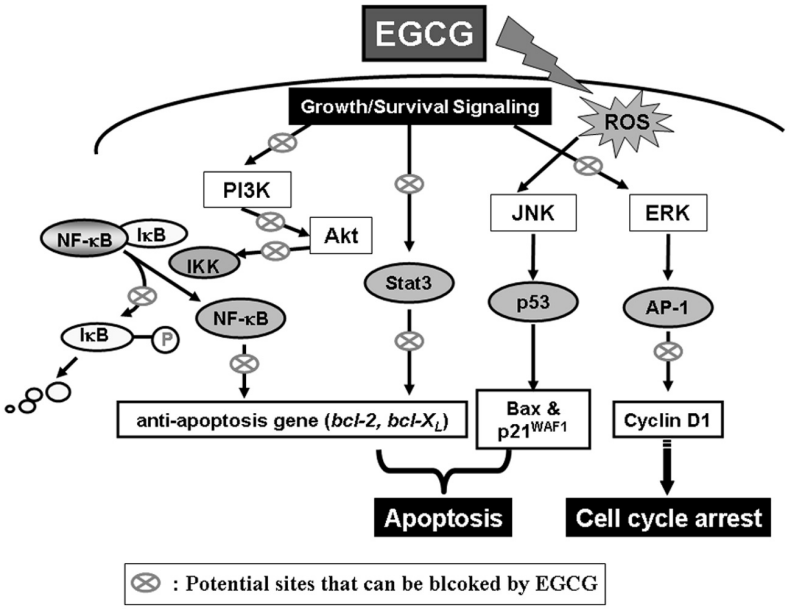

Figure 2. Signal transduction pathways mediating EGCG-induced apoptosis and cell cycle arrest.

unresolved. Recent studies have revealed the presence of a *cis*-acting element known as antioxidant/electrophile response element (ARE/EpRE) located in the promoter region of many of the antioxidants genes. Expression of majority of antioxidant enzymes is regulated by activation of nuclear factor erythroid 2 p45 (NF-E2)-related factor (Nrf2) [24]. EGCG has been known as the most potent ARE-luciferase inducer among the green tea polyphenols [25]. EGCG activates some mitogen-activated protein kinases (MAPK), which in turn phosphorylates Nrf2, facilitating its dissociation from the Keap1. EGCG may acts as a mind pro-oxidant depending on the cellular environment, generating ROS that can oxidize the cysteine thiol of Keap1, releasing Nrf2. Figure 1 illustrates the proposed mechanisms by which EGCG activates Nrf2, leading to upregulation of ARE-driven antioxidant gene expression.

3.2 Growth inhibition and cell cycle arrest

Deregulated cell cycle is characteristic of malignant or transformed cells. EGCG inhibited the cell cycle progression in various types of cancer cells [26–32]. EGCG-induced cell cycle dysregulation is mediated via modulation of cyclin dependent kinase inhibitor-cyclin-cdk machinery [33]. This can be achieved by (i) upregulation of the cyclin dependent kinase inhibitors such as p21WAF1, p27KIP1, p16INK4a, p18INK4b; (ii) suppression of protein expression of cyclin D1, cyclin E, cdk2, cdk4, and cdk6; (iii) enhancement of the binding of cyclin D1 to p21WAF1 and p27KIP1; (iv) inhibition of binding of cyclin E to cdk2; (v) downregulation of phosphorylation of retinoblastoma tumor suppressor protein.

Epidermal growth factor receptor (EGFR) and human EGFR-2 (Her-2) are frequently constitutively activated/overexpressed in several cancer cell lines. EGCG inhibited the phosphorylation of EGFR and HER2 proteins and subsequently ERK and AKT proteins in human colon cancer HT29 cells [34]. Under the same experimental conditions, EGCG inhibited transcriptional activity of cyclin D1 promoter. EGCG inhibited the growth and the transformed phenotype of MMTV-Her-2/neu mouse mammary tumor derived cells (NF639) by blocking the basal Her-2/nue receptor tyrosine phosphorylation and eventually the phosphatidylinositol 3-kinase-AKT and NF-κB signaling [35]. EGCG inhibited growth factor-dependent activation of epidermal growth factor receptor (EGFR) and its downstream target molecules, such as ERK and AKT in immortalized cervical cells [36]. These changes were associated with elevated levels of p53, p21WAF1 and p27KIP1, while the cyclin E1 level and CDK2 kinase activity were reduced. Consistent with these findings, flow cytometric analysis revealed the EGCG-mediated G1 arrest, while sustained EGCG treatment caused apoptotic death. In another study, EGCG inhibited the phosphatidylinositol 3-kinase-AKT signaling in both androgen-responsive and -unresponsive human prostate cancer cell lines [37].

Transcription of cyclin D1 is regulated by both the ERK [38] and signal transducer and activator of transcription 3 (Stat3) signaling pathways [39]. A major target of ERK and Stat3 is AP-1 [38, 40] (Fig. 2). The inhibition of AP-1 activity by EGCG has also been revealed in several studies [41–43].

3.3 Induction of cancer cell apoptosis

The disruption of regulation of apoptosis is observed in a variety of cancers. Induction of apoptosis is hence considered as an important mechanism by which damaged cells

are eliminated before malignancy manifests. Apoptosis induction by EGCG is more prominent in cancer cells than in normal cells because NF-κB is activated in the cancer cells compared to normal cells [44–46]. EGCG-induced apoptosis of cancer cells may be mediated through NF-κB inactivation [45] as illustrated in Fig. 2. Several recent studies demonstrated that the inactivation of NF-κB by EGCG was associated with inhibition of IκB-kinase (IKK) activity, enhancement of phosphorylation-dependent degradation of IκBα and subsequent increases in nuclear translocation of p65 protein [45, 47]. However, EGCG inhibited lipopolysaccharide (LPS)-induced phosphorylation of IκBα, but failed to affect NF-κB luciferase reporter gene activation in human colon cancer (HT-29) cells [48], suggesting that EGCG modulation of NF-κB transcriptional activity is not necessarily dependent on IκBα degradation and subsequent release of NF-κB proteins. Okabe *et al*. [49] have suggested that EGCG down-regulates the NF-κB inducing kinase (NIK) expression in human lung cancer cell PC-9. Activation of NF-κB promotes transcriptional up-regulation of Bcl-2 and Bcl-X_L [50]. Negative regulation of NF-κB by EGCG decreases the expression of the proapoptotic protein Bcl-2. EGCG abrogated the expression of anti-apoptotic Bcl-2 and Bcl-X_L proteins and enhanced the levels pro-apoptotic Bax proteins followed by caspase-3 activation [51, 52].

In addition to NF-κB, Stat3 can upregulate the expression of Bcl-X_L and Bcl-2 [53]. Therefore, inhibition of Stat3 by EGCG may account for the decrease in the levels of the Bcl-X_L and Bcl-2 proteins, while the precise mechanism by which EGCG causes an increase in the level of the Bax protein remains to be determined. EGCG treatment resulted in the stabilization of p53 via phosphorylation of critical serine residues on this tumor suppressor and modulation of the MDM2-p14ARF pathway, which sensitized the cells to EGCG-mediated apoptosis through activation of its downstream targets p21WAF1 and Bax [51]. Thus, EGCG can target three important transcription factors p53, Stat3, and NF-κB in exerting its proapoptotic effects in cancer cells (Fig. 2).

Lei *et al*. [54] have reported that JNK signaling is necessary for stress-induced release of cytochrome *c* and programmed cell death. Apoptosis induction by EGCG was associated with activation of JNK in HT-29 human colon cancer [55], pancreatic cancer [56], and human leukemic cells [57]. Moreover, activation of p38 MAPK, MAPK kinase (MKK) 3/6, MAPK kinase 4 and apoptosis signal-regulating kinase 1 (ASK1) is involved in EGCG-induced apoptosis in human leukemic U937 and OCI-AML cells [57].

Proapoptotic activity of EGCG may be associated with intracellular accumulation of ROS. At normal physiological pH, EGCG may undergo auto-oxidation to form dimers, accompanying the generation of ROS due to chemical reactions of the polyphenolic groups [46, 58]. Antioxidant *N*-acetyl-L-cysteine suppressed the production of intracellular ROS and apoptosis through blockade of activation of MAPK induced by EGCG [55–57]. Moreover, it has been reported that EGCG-induced apoptosis was mediated via production of H_2O_2 [46, 58]. ROS can promote cytochrome *c* release to the cytosol by stimulating its dissociation from cardiolipin, an inner mitochondrial membrane phospholipid component [59]. Therefore, EGCG-induced ROS may initiate the apoptosis signaling cascade (Fig. 2).

3.4 Inhibition of inflammation or tumor promotion

Of the multiple protective effects of EGCG on carcinogenesis, its anti-tumor promotional capability is of particular interest. Besides inhibiting phorbol-12-myristate-13-acetate (PMA)-induced mouse papilloma formation, EGCG affects some of the biochemical events associated with tumor promotion. Inflammation has been considered to be a critical event in tumor promotion [15]. Persistent inflammation creates an abnormal microenvironment where a distinct set of proinflammatory mediators promote neoplastic transformation of cells. Therefore, one of the plausible actions of chemopreventive phytochemicals would be the suppression of abnormal over-production of pro-inflammatory mediators such as interleukin (IL), tumor necrosis factor (TNF)-α, and prostaglandins (PG), especially PGE_2 and $PGF_{2\alpha}$. In response to inflammatory stimuli, PG are produced in abundance through metabolic conversion of arachidonic acid by the enzyme cyclooxygenase-2 (COX-2), which is inappropriately upregulated in various premalignant and malignant tissues. Moreover, COX-2 overexpressing transgenic mice are highly susceptible to spontaneous tumor formation [60], while COX-2 knockout animals are less prone to experimentally induced tumorigenesis [61]. Inhibition of COX-2 is hence considered as one of the most promising strategies for cancer prevention and treatment.

Several *in vivo* and *in vitro* studies revealed that EGCG suppressed COX-2 expression in response to tumor promoter [62] and other stimuli [63–65]. EGCG also significantly inhibits the *N*-nitrosomethylbenzylamine-induced rat esophageal carcinogenesis as well as PGE_2 production [65]. EGCG-mediated COX-2 downregulation was associated with inhibition of ERK1/2 and p38 MAPK in 2,2′-azobis(2-amidinopropane)dihydrochloride-induced human keratinocyte cells [63] and PMA-induced mouse skin [62]. Oral administration of EGCG inhibited activation of NF-κB that is an important transcription factor to regulate COX-2 expression in mouse skin *in vivo* [62].

Another essential proinflammatory factor contributing to tumor promotion is TNFα [66]. EGCG inhibited TNFα

mRNA expression in macrophage (RAW264.7) cells [67], keratinocytes [68] and BALB/3T3 cells [69] stimulated with LPS, UVB and okadaic acid, respectively. EGCG also attenuated gene expression and release of IL8 in normal human keratinocytes [70] and human airway (A549) cells [71] stimulated with TNFα and IL1β, respectively. EGCG downregulates TNFα gene expression by inactivating NF-κB pathway [67, 68]. Likewise, EGCG inhibited the expression of inducible nitric oxide synthase and production of nitric oxide in IL1β-treated human chondrocytes [72] and LPS-stimulated murine peritoneal macrophages [73] through inactivation of NF-κB.

3.5 Inhibition of migration of cancer cells

Invasion and metastasis are crucial steps in cancer progression. Invasiveness of tumor cells strongly depends on their ability to migrate and to adhere to their extracellular matrix (ECM) environment. Adhesive interactions between tumor cells and ECM protein, such as collagen, fibronectin, and laminin, are deeply involved in tumor growth, invasion and metastasis [74]. Angiogenesis is also pivotal in the progression of carcinogenesis. Autocrine and paracrine factors such as fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), transforming growth factor (TGFβ), are important molecules involved in controlling tumor angiogenesis [75]. In addition, the urokinase plasminogen-plasmin system and the matrix metalloproteinases (MMP) that degrade collagen and other extracellular matrix proteins play an important role in tumor progression, metastasis, vascular remodeling, and angiogenesis [76–79].

EGCG has been reported to prevent metastasis [80–82], angiogenesis [83, 84], and invasion [85, 86]. The molecular mechanism of anti-angiogenesis, anti-invasion, and anti-metastasis by EGCG is not clearly elucidated at present. Inhibitory effects of EGCG on expression or activity of MMP [80, 83, 85, 87–90], VEGF [88, 91, 92], and focal adhesion kinase [80] as well as inhibition of phosphorylation of EGFR and platelet-derived growth factor receptor [93] have been demonstrated.

EGCG also upregulated the expression of tissue inhibitor of MMP (TIMP) [83, 86, 94]. It has been reported that urokinase, one of the hydrolases implicated in the degradation of the extracellular matrix and tumor invasion, is directly inhibited by EGCG [95]. Urokinase-type plasminogen activator (uPA) and the uPA receptor form a complex proteolytic system that mediates tumor invasion and metastasis. EGCG was found to be a potent suppressor of uPA expression in human fibrosarcoma HT 1080 cells [96]. In addition, EGCG inhibited uPA promoter activity and also destabilized uPA mRNA. EGCG-induced suppression of uPA promoter activity as well as expression appears to be mediated by blocking ERK and p38 MAPK, but not JNK and AKT [96].

Moreover, EGCG inhibits MMP-2 and MMP-9 activities, resulting in the inhibition of *in vitro* tumor cell invasion [86, 89]. MMP-2 is secreted as pro-MMP-2, which can be activated by MT1-MMP through cleavage of its propeptide [97]. EGCG inhibited the gelatinolytic activity of MMP-2 [98] by inhibiting the conversion of pro-MMP-2 into an activated form [85] or downregulation of MT1-MMP [89, 99], which led to inhibition of invasion of smooth muscle cells. It has been known that inhibition of MAPK suppresses the MMP expression. Simon *et al*. [100] demonstrated that PMA-enhanced MMP-9 secretion and *in vitro* invasiveness were associated with a strong activation of p38 MAPK. Kurata *et al*. [101] have reported that constitutive activation of MAPK kinase is critical and sufficient for the activation of MMP-2. EGCG treatment decreased the levels of phospho-ERK1/2, phospho-MEK1/2, and p38 MAPK [89, 102].

Additionally, EGCG blocked the adhesion of mouse melanoma B16 cells to laminin, which is involved in the release of type IV collagenase responsible for cancer invasion and metastasis from malignant cells [103]. Integrin-mediated cell adhesion induces tyrosine phosphorylation of focal adhesion kinase [104], which represents a key event in signaling for cell movement, cell adhesion, and anchorage-independent growth [105]. EGCG significantly inhibited the tyrosine phosphorylation of focal adhesion kinase and activity of MMP-9. There are binding sites for both AP-1 and NF-κB in the conserved regions of the rabbit MMP-9 gene promoter [106]. In addition, several growth factor and cytokine regulatory pathways converge at the AP-1 and NF-κB binding site. EGCG inhibited the activation of AP-1 and NF-κB induced by epidermal growth factor, PMA and LPS [47, 48, 107]. EGCG inhibited medulloblastoma cell migration specifically on collagen by increasing cell adhesive ability through upregulation of the β1 integrin subunit [108]. EGCG also inhibited VEGF production by inhibiting both constitutive activation of Stat 3 and NF-κB, but not ERK or AKT in human breast and head and neck cancer cell lines [91].

4 Conclusion

Although there is no magic bullet to completely cure cancer at this moment, we are now aware of the fact that many forms of cancers are at least avoidable or preventable. Remarkable progress in unfolding cancer biology in recent years led us to find several ways to intervene in carcinogenic process. Transcription factors, such as NF-κB and AP-1, and their upstream signal regulators are considered to play a central role in regulating the cell proliferation,

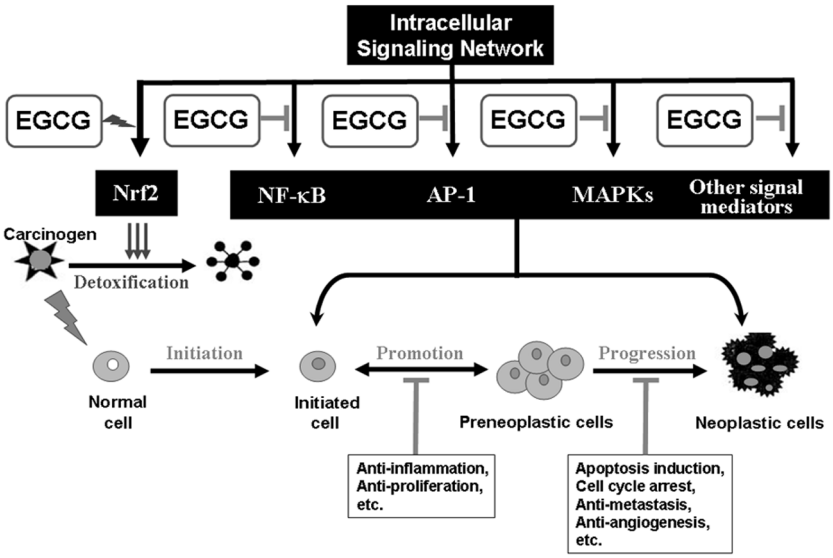

Figure 3. Possible molecular targets for chemopreventive effects of EGCG on multi-stage carcinogenesis.

invasion, and metastasis. In this context, blockade of abnormal or improper activation of these signal network molecules might provide ample opportunities for cancer chemoprevention. Targeted suppression of inappropriately activated NF-κB or AP-1 can ameliorate proinflammatory, proliferative, invasive, and metastastic signals. EGCG has been shown to inhibit the activation of NF-κB and AP-1, which may account for its anti-proliferative, proapoptotic, anti-metastatic and anti-angiogenic activities in cancer cells as well as anti-tumor promotional effects. In addition, EGCG stimulates the detoxification process via Nrf2-mediated *de novo* synthesis of antioxidant or phase-II enzymes while inhibiting metabolic activation of carcinogens, thereby interfering with the tumor initiation. Therefore, the modulation of signal transduction pathways implicated in multi-stage carcinogenesis by EGCG may represent an important component in molecular target-based chemoprevention by this dietary phytochemical (Fig. 3).

This work was supported by the research grant (awarded to Y.-J. Surh) for Functional Food Research and Development from the Korea Science and Engineering Foundation, Republic of Korea.

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